10/032,897

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Term: L4 and misincorporat$3

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DB=USPT,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L5	L4 and misincorporat$3	3	L5
L4	L3 and virus$2	65	L4
L3	L2 and resistan$2	66	L3
L2	L1 and agent$1	95	L2
L1	quasispecies	111	L1

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. 6297003 . 18 Jul 97; 02 Oct 01. Methods for the detection of a novel hepatitis C virus (HCV) terminal 3' noncoding region. Rice; Charles M., et al. 435/5; 435/6 536/24.3 536/24.33. C12Q001/70.

☐ 2. 5874565 . 29 Aug 95; 23 Feb 99. Nucleic acids comprising a highly conserved novel 3 terminal sequence element of the hepatitis C virus. Rice; Charles M., et al. 536/24.1; 435/366 435/370 435/6 536/23.1 536/24.3 536/24.33. C07H021/02 C07H021/04 C12Q001/68 C12N015/00.

☐ 3. 5728519 . 21 Dec 94; 17 Mar 98. Assay for virulent revertants of attenuated live vaccines and kits therefor. Levenbook; Inessa S., et al. 435/5; 424/130.1 424/131.1 424/184.1 424/193.1 424/199.1 424/204.1 424/205.1 424/217.1 424/520 424/93.1 424/93.2 435/235.1 435/236 435/237 435/239 435/6 435/7.1 435/91.1 435/91.2 435/91.5 435/948 436/501 436/543 436/547 436/8 436/811 436/819 536/2 3.1 536/24.1 536/24.3 536/24.31 536/24.32 536/24.33. C12Q001/68.

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Term	Documents
MISINCORPORAT$3	0
MISINCORPORATE	8
MISINCORPORATED	95
MISINCORPORATES	5
MISINCORPORATING	2
MISINCORPORATION	353
(MISINCORPORAT$3 AND 4).USPT,JPAB,EPAB,DWPI.	3
(L4 AND MISINCORPORAT$3).USPT,JPAB,EPAB,DWPI.	3

Previous Page Next Page

10/032897

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FILE 'HOME' ENTERED AT 12:23:23 ON 14 AUG 2003

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COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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=> s quasi-species(10a)agent#
L1 2 QUASI-SPECIES(10A) AGENT#

=> s l1 and resistan##
L2 1 L1 AND RESISTAN##

=> d l2 bib ab kwic

L2 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:487349 BIOSIS
DN PREV200200487349
TI Process and **agent** for instabilizing viral **quasi-species**-distributions avoiding **resistance** phenomena.
AU Eigen, Manfred (1); Schwienhorst, Andreas; Biebricher, Christof; Lindemann, Bjorn; Domingo, Esteban; Holland, John; Henco, Karsten
CS (1) Gottingen Germany
ASSIGNEE: Evotec BioSystems AG, Hamburg, Germany
PI US 6423516 July 23, 2002
SO Official Gazette of the United States Patent and Trademark Office Patents, (July 23, 2002) Vol. 1260, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133.
DT Patent
LA English
AB A process for instabilizing viral quasi-species-distributions under avoidance of **resistance** phenomena by replication of the nucleic acids of the viruses present in the quasi-species-distribution by of a defective replication system, a) whereby the defective replication system has a rate of misincorporation for nucleotides above the rate of misincorporation of the viral wild-type-replication system and, whereby the viruses are replicated by the replication system having the higher rate of misincorporation at least as effectively as it is done by the replication system of the wild-type virus, b) and/or negative influence of the replication of the consensus-sequence (nucleic acid sequence of the wild-type virus) in relation to other replicatable nucleic acids.
TI Process and **agent** for instabilizing viral **quasi-species**-distributions avoiding **resistance** phenomena.
AB A process for instabilizing viral quasi-species-distributions under avoidance of **resistance** phenomena by replication of the nucleic acids of the viruses present in the quasi-species-distribution by of a defective replication system,. . .
IT Miscellaneous Descriptors

defective replication system: nucleotide misincorporation rate; **resistance** phenomena avoidance; viral quasi-species-distributions: instabilizing process

```
=> s quasi species and agent# and resistan##
L3          32 QUASI SPECIES AND AGENT# AND RESISTAN##

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4           20 DUP REM L3 (12 DUPLICATES REMOVED)

=> s l4 and replicat###
L5          10 L4 AND REPLICAT###

=> s l5 and misincorporat###
L6           1 L5 AND MISINCORPORAT###

=> d l6 bib ab kwic

L6   ANSWER 1 OF 1  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN   2002:487349  BIOSIS
DN   PREV200200487349
TI   Process and agent for instabilizing viral quasi-
     species-distributions avoiding resistance phenomena.
AU   Eigen, Manfred (1); Schwienhorst, Andreas; Biebricher, Christof;
     Lindemann, Bjorn; Domingo, Esteban; Holland, John; Henco, Karsten
CS   (1) Gottingen Germany
     ASSIGNEE: Evotec BioSystems AG, Hamburg, Germany
PI   US 6423516 July 23, 2002
SO   Official Gazette of the United States Patent and Trademark Office Patents,
     (July 23, 2002) Vol. 1260, No. 4, pp. No Pagination.
     http://www.uspto.gov/web/menu/patdata.html. e-file.
     ISSN: 0098-1133.
DT   Patent
LA   English
AB   A process for instabilizing viral quasi-species
     -distributions under avoidance of resistance phenomena by
     replication of the nucleic acids of the viruses present in the
     quasi-species-distribution by of a defective
     replication system, a) whereby the defective replication
     system has a rate of misincorporation for nucleotides above the
     rate of misincorporation of the viral wild-type-
     replication system and, whereby the viruses are replicated
     by the replication system having the higher rate of
     misincorporation at least as effectively as it is done by the
     replication system of the wild-type virus, b) and/or negative
     influence of the replication of the consensus-sequence (nucleic
     acid sequence of the wild-type virus) in relation to other replicatable
     nucleic acids.
TI   Process and agent for instabilizing viral quasi-
     species-distributions avoiding resistance phenomena.
AB   A process for instabilizing viral quasi-species
     -distributions under avoidance of resistance phenomena by
     replication of the nucleic acids of the viruses present in the
     quasi-species-distribution by of a defective
     replication system, a) whereby the defective replication
     system has a rate of misincorporation for nucleotides above the
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     replication system and, whereby the viruses are replicated
     by the replication system having the higher rate of
     misincorporation at least as effectively as it is done by the
     replication system of the wild-type virus, b) and/or negative
     influence of the replication of the consensus-sequence (nucleic
```

acid sequence of the wild-type virus) in relation to other replicatable nucleic acids.

IT Miscellaneous Descriptors
defective **replication** system: nucleotide **misincorporation** rate; **resistance** phenomena avoidance; viral **quasi-species**-distributions: instabilizing process

=> d l5 1-10 bib ab kwic

L5 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:824300 CAPLUS
DN 136:100731
TI Effect of HCV viral dynamics on treatment design: Lessons learned from HIV
AU Bain, Vincent G.
CS Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, AB, Can.
SO American Journal of Gastroenterology (2001), 96(10), 2818-2828
CODEN: AJGAAR; ISSN: 0002-9270
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A review. Viral load measurements provide an indication of viral **replication**, and thereby serve as a valuable tool to guide the initiation of therapy and subsequent changes. Plasma human immunodeficiency viral load strongly predicts the rate of decrease in CD4+ lymphocyte count, and progression to AIDS and death. Furthermore, the efficacy of antiretroviral therapy can be assessed by monitoring changes in plasma human immunodeficiency viral load. Similarly, viral load provides valuable information about the natural history of the hepatitis C virus infection. Hepatitis C viral load can be used to predict the likelihood of response to std. interferon-.alpha. treatment and other interferon-.alpha. regimens and to monitor treatment efficacy. Increased understanding of the natural history of the hepatitis C virus infection and the nature of **resistance** to interferon-.alpha. therapy suggests that effective treatment regimens must maintain serum levels of interferon-.alpha.. Ideally, interferon-.alpha. serum levels should provide const. pressure on the virus and should prevent viral rebound, thereby avoiding continued viral **replication** and minimizing the potential for emergence of **resistant quasi-species**. Current regimens designed to address these points include early aggressive intervention, combination drug regimens, prolonged maintenance, and novel interferons. By enabling the design and rapid assessment of new treatment regimens, viral load measurement will revolutionize the clin. management of the hepatitis C virus infection, as it has the HIV.
RE.CNT 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review. Viral load measurements provide an indication of viral **replication**, and thereby serve as a valuable tool to guide the initiation of therapy and subsequent changes. Plasma human immunodeficiency viral load strongly predicts the rate of decrease in CD4+ lymphocyte count, and progression to AIDS and death. Furthermore, the efficacy of antiretroviral therapy can be assessed by monitoring changes in plasma human immunodeficiency viral load. Similarly, viral load provides valuable information about the natural history of the hepatitis C virus infection. Hepatitis C viral load can be used to predict the likelihood of response to std. interferon-.alpha. treatment and other interferon-.alpha. regimens and to monitor treatment efficacy. Increased understanding of the natural history of the hepatitis C virus infection and the nature of **resistance** to interferon-.alpha. therapy suggests that effective treatment regimens must maintain serum levels of interferon-.alpha.. Ideally, interferon-.alpha. serum levels should

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IT Antiviral **agents**
Hepatitis C virus
Human
Human immunodeficiency virus
(effect of HCV viral dynamics on treatment design in humans using lessons learned from HIV)

L5 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:490145 CAPLUS
DN 135:282733
TI Changes in human immunodeficiency virus type 1 populations after treatment interruption in patients failing antiretroviral therapy
AU Hance, Allan J.; Lemiale, Virginie; Izopet, Jacques; Lecossier, Denise; Joly, Veronique; Massip, Patrice; Mammano, Fabrizio; Descamps, Diane; Brun-Vezinet, Francoise; Clavel, Francois
CS INSERM U552, Hopital Bichat-Claude Bernard, Paris, 75018, Fr.
SO Journal of Virology (2001), 75(14), 6410-6417
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
AB Mutations in human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and protease that confer **resistance** to antiretroviral **agents** are usually accompanied by a redn. in the viral **replicative** capacity under drug-free conditions. Consequently, when antiretroviral treatment is interrupted in HIV-1-infected patients harboring drug-**resistant** virus, **resistant quasi-species** appear to be most often replaced within several weeks by wild-type virus. Using a real-time PCR-based technique for the selective quantification of **resistant** viral sequences in plasma, we have studied the kinetics of the switch from mutant to wild-type virus and evaluated the extent to which minority populations of **resistant** viruses not detected by genotyping persist in these individuals. Among 12 patients with viruses expressing the V82A or L90M **resistance** mutation who had undergone a 3-mo interruption of therapy and for whom conventional genotyping had revealed an apparent total reconversion to wild-type virus, minority populations expressing these mutations, representing 0.1 to 21% of total virus, were still detectable in 9 cases. Kinetic studies demonstrated that viruses expressing **resistance** mutations could be detected for >5 mo after the discontinuation of treatment in some patients. Most of the minority **resistant** genomes detected more than 3 mo after the interruption of therapy carried only part of the mutations present in the **resistant** viruses prior to treatment interruption and appeared to result from the emergence of existing strains selected at earlier stages in the development of drug **resistance**. Thus, following the interruption of treatment, viral populations contg. **resistance** mutations can persist for several months after the time when conventional genotyping techniques detect only wild-type virus. These populations include viral strains with only some of the **resistance** mutations initially present, strains that presumably express better fitness under drug-free conditions.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Mutations in human immunodeficiency virus type 1 (HIV-1) reverse

transcriptase and protease that confer **resistance** to antiretroviral **agents** are usually accompanied by a redn. in the viral **replicative** capacity under drug-free conditions. Consequently, when antiretroviral treatment is interrupted in HIV-1-infected patients harboring drug-**resistant** virus, **resistant quasi-species** appear to be most often replaced within several weeks by wild-type virus. Using a real-time PCR-based technique for the selective quantification of **resistant** viral sequences in plasma, we have studied the kinetics of the switch from mutant to wild-type virus and evaluated the extent to which minority populations of **resistant** viruses not detected by genotyping persist in these individuals. Among 12 patients with viruses expressing the V82A or L90M **resistance** mutation who had undergone a 3-mo interruption of therapy and for whom conventional genotyping had revealed an apparent total reconversion to wild-type virus, minority populations expressing these mutations, representing 0.1 to 21% of total virus, were still detectable in 9 cases. Kinetic studies demonstrated that viruses expressing **resistance** mutations could be detected for >5 mo after the discontinuation of treatment in some patients. Most of the minority **resistant** genomes detected more than 3 mo after the interruption of therapy carried only part of the mutations present in the **resistant** viruses prior to treatment interruption and appeared to result from the emergence of existing strains selected at earlier stages in the development of drug **resistance**. Thus, following the interruption of treatment, viral populations contg. **resistance** mutations can persist for several months after the time when conventional genotyping techniques detect only wild-type virus. These populations include viral strains with only some of the **resistance** mutations initially present, strains that presumably express better fitness under drug-free conditions.

ST antiretroviral HIV antiAIDS antiviral **resistance** genotype

IT Drug **resistance**
(antiviral; changes in HIV-1 populations after treatment interruption in humans failing antiretroviral therapy)

IT Anti-AIDS **agents**
Genotypes
Genotyping (method)
Human immunodeficiency virus 1
Mutation
(changes in HIV-1 populations after treatment interruption in humans failing antiretroviral therapy)

IT Antiviral **agents**
(**resistance** to; changes in HIV-1 populations after treatment interruption in humans failing antiretroviral therapy)

L5 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2000:298864 CAPLUS
DN 133:308746

TI Physiopathology and treatment of acquired immunodeficiency syndrome

AU Soto Ramirez, Luis Enrique
CS Departamento de Infectologia. Instituto Nacional de Nutricion Salvador Zubiran, Mex.

SO Revista de Investigacion Clinica (2000), 52(1), 60-71
CODEN: RICLAG; ISSN: 0034-8376
PB Instituto Nacional de la Nutricion Salvador Zubiran
DT Journal; General Review
LA Spanish

AB A review with 65 refs. The last pandemic of the century, that of AIDS caused by the human immunodeficiency virus (HIV), continues to advance with gigantic steps at about 18,000 new infections per day worldwide. In the last 4 yr, breakthroughs have been achieved and new medications have been introduced, which have impacted the progression of HIV and its disease, decreasing assocd. morbidity and mortality. During the course of infection, HIV **replicates** actively producing as much as 1010

genetically different virions (**quasi-species**), which relates to immune escape, higher pathogenicity, and drug **resistance**. Persistent viral **replication** causes T CD4+ cell destruction and immunodeficiency through several mechanisms. Currently, there are 14 approved anti-retrovirals that when used as triple regimens have been able to decrease opportunistic infections, hospitalization, and mortality rates. Unfortunately, these regimens still have many limitations, do not cure, and can only suppress the virus effectively in 50% of the treated patients. Besides, when they are inadequately used there is assocd. **resistance** development. However, indications for treatment initiation are changing continuously and heading towards a conservative approach. In the case of salvage regimens, there are only general guidelines that have not been evaluated in clin. studies. **Resistance** assays have great limitations and their use is very specific. All these factors have made the anti-retroviral therapy a very complicated issue.

RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 65 refs. The last pandemic of the century, that of AIDS caused by the human immunodeficiency virus (HIV), continues to advance with gigantic steps at about 18,000 new infections per day worldwide. In the last 4 yr, breakthroughs have been achieved and new medications have been introduced, which have impacted the progression of HIV and its disease, decreasing assocd. morbidity and mortality. During the course of infection, HIV **replicates** actively producing as much as 1010 genetically different virions (**quasi-species**), which relates to immune escape, higher pathogenicity, and drug **resistance**. Persistent viral **replication** causes T CD4+ cell destruction and immunodeficiency through several mechanisms. Currently, there are 14 approved anti-retrovirals that when used as triple regimens have been able to decrease opportunistic infections, hospitalization, and mortality rates. Unfortunately, these regimens still have many limitations, do not cure, and can only suppress the virus effectively in 50% of the treated patients. Besides, when they are inadequately used there is assocd. **resistance** development. However, indications for treatment initiation are changing continuously and heading towards a conservative approach. In the case of salvage regimens, there are only general guidelines that have not been evaluated in clin. studies. **Resistance** assays have great limitations and their use is very specific. All these factors have made the anti-retroviral therapy a very complicated issue.

IT AIDS (disease)
Anti-AIDS **agents**
(physiopathol. and treatment of acquired immunodeficiency syndrome)

L5 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:414400 CAPLUS
DN 129:156495
TI Preclinical characterization of an anti-tat ribozyme for therapeutic application
AU Wang, Li; Witherington, Craig; King, Andrew; Gerlach, Wayne L.; Carr, Andrew; Penny, Ron; Cooper, David; Symonds, Geoff; Sun, Lun-Quan
CS Johnson and Johnson Research Laboratories, Sydney, NSW 2001, Australia
SO Human Gene Therapy (1998), 9(9), 1283-1291
CODEN: HGTHE3; ISSN: 1043-0342
PB Mary Ann Liebert, Inc.
DT Journal
LA English
AB A hammerhead ribozyme retroviral construct, denoted RRz2, targeting the coding region of the human immunodeficiency virus type 1 (HIV-1) tat gene, has shown itself to be effective in a range of test systems. Inhibition of the **replication** of HIV-1 IIIB and primary drug-**resistant** strains in pooled transduced CEMT4 cells was consistently found to be more than 80% compared with the control-vector

transduced cells, whereas a mutant RRz2 gave approx. 45% inhibition. A multiple HIV-1 passage assay showed the absence of emergence of mutations within the specific viral RNA ribozyme target sequences. This lack of generation of ribozyme "escape mutants" occurred despite the almost complete disappearance of a HIV-1 **quasi-species** in the testing virus. When RRz2 was tested in peripheral blood lymphocytes (PBLs) from HIV-1-infected patients, paired anal. showed that cell viability in the ribozyme-transduced HIV-1-infected PBLs was significantly higher than that in the vector-transduced cells. This difference in viability (vector vs. RRz2) was not obsd. in PBLs from non-HIV-1-infected donors. Taken together, these results indicate that the transfer of an anti-HIV-1 ribozyme gene into human T lymphocytes could have major impact on viral **replication** and T cell viability in the HIV-1-infected individual.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A hammerhead ribozyme retroviral construct, denoted RRz2, targeting the coding region of the human immunodeficiency virus type 1 (HIV-1) tat gene, has shown itself to be effective in a range of test systems. Inhibition of the **replication** of HIV-1 IIIB and primary drug-**resistant** strains in pooled transduced CEMT4 cells was consistently found to be more than 80% compared with the control-vector transduced cells, whereas a mutant RRz2 gave approx. 45% inhibition. A multiple HIV-1 passage assay showed the absence of emergence of mutations within the specific viral RNA ribozyme target sequences. This lack of generation of ribozyme "escape mutants" occurred despite the almost complete disappearance of a HIV-1 **quasi-species** in the testing virus. When RRz2 was tested in peripheral blood lymphocytes (PBLs) from HIV-1-infected patients, paired anal. showed that cell viability in the ribozyme-transduced HIV-1-infected PBLs was significantly higher than that in the vector-transduced cells. This difference in viability (vector vs. RRz2) was not obsd. in PBLs from non-HIV-1-infected donors. Taken together, these results indicate that the transfer of an anti-HIV-1 ribozyme gene into human T lymphocytes could have major impact on viral **replication** and T cell viability in the HIV-1-infected individual.

IT Antiviral **agents**
Gene therapy
Human immunodeficiency virus 1
Retroviral vectors
Retroviridae
(preclin. characterization of anti-tat ribozyme for therapeutic application in HIV-1 infection)

L5 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:487349 BIOSIS
DN PREV200200487349
TI Process and **agent** for instabilizing viral **quasi-species**-distributions avoiding **resistance** phenomena.
AU Eigen, Manfred (1); Schwienhorst, Andreas; Biebricher, Christof; Lindemann, Bjorn; Domingo, Esteban; Holland, John; Henco, Karsten
CS (1) Gottingen Germany
ASSIGNEE: Evotec BioSystems AG, Hamburg, Germany
PI US 6423516 July 23, 2002
SO Official Gazette of the United States Patent and Trademark Office Patents, (July 23, 2002) Vol. 1260, No. 4, pp. No Pagination.
http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DT Patent
LA English
AB A process for instabilizing viral **quasi-species**-distributions under avoidance of **resistance** phenomena by **replication** of the nucleic acids of the viruses present in the **quasi-species**-distribution by of a defective

replication system, a) whereby the defective **replication** system has a rate of misincorporation for nucleotides above the rate of misincorporation of the viral wild-type-**replication** system and, whereby the viruses are **replicated** by the **replication** system having the higher rate of misincorporation at least as effectively as it is done by the **replication** system of the wild-type virus, b) and/or negative influence of the **replication** of the consensus-sequence (nucleic acid sequence of the wild-type virus) in relation to other replicatable nucleic acids.

TI Process and **agent** for instabilizing viral **quasi-species**-distributions avoiding **resistance** phenomena.

AB A process for instabilizing viral **quasi-species** -distributions under avoidance of **resistance** phenomena by **replication** of the nucleic acids of the viruses present in the **quasi-species**-distribution by of a defective **replication** system, a) whereby the defective **replication** system has a rate of misincorporation for nucleotides above the rate of misincorporation of the viral wild-type-**replication** system and, whereby the viruses are **replicated** by the **replication** system having the higher rate of misincorporation at least as effectively as it is done by the **replication** system of the wild-type virus, b) and/or negative influence of the **replication** of the consensus-sequence (nucleic acid sequence of the wild-type virus) in relation to other replicatable nucleic acids.

IT Miscellaneous Descriptors
defective **replication** system: nucleotide misincorporation rate; **resistance** phenomena avoidance; viral **quasi-species**-distributions: instabilizing process

L5 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 2002:298017 BIOSIS

DN PREV200200298017

TI Selection of drug-**resistant** HIV-1 mutants in response to repeated structured treatment interruptions.

AU Martinez-Picado, Javier (1); Morales-Lopetegi, Kristina; Wrin, Terri; Prado, Julia G.; Frost, Simon D. W.; Petropoulos, Christos J.; Clotet, Bonaventura; Ruiz, Lidia

CS (1) Hospital Germans Trias i Pujol, IrsiCaixa Foundation, Ctra. de Canyet s/n, 08916, Badalona: javiermp@ns.hugtip.scs.es Spain

SO AIDS (Hagerstown), (12 April, 2002) Vol. 16, No. 6, pp. 895-899. http://www.aidsonline.com/. print.
ISSN: 0269-9370.

DT Article

LA English

AB Background A new HIV-1 treatment strategy based on repeated structured treatment interruptions (STI) is currently being evaluated in clinical trials to determine whether immune cell-mediated control of viral **replication** can be stimulated by intermittent periods of viral **replication**. The potential for selection of drug-**resistant** **quasi-species** remains a major concern of such a treatment strategy. Methods Plasma and peripheral blood lymphocyte (PBL) samples from 12 patients who had three consecutive STIs were studied. Genotypic analysis was based on population and clonal sequencing. Drug susceptibility and their corresponding **replication** capacities were evaluated by a single-cycle growth assay. Results Consistent with a loss of phenotypic susceptibility to lamivudine, the M184V mutation was detected by genotypic analysis (direct and clonal sequencing) in plasma samples collected from two patients at the end of the second or third STI. Longitudinal analysis of patient samples revealed a step-wise increase in the M184V mutation in each patient virus population over successive STIs, despite the lower **replicative** capacity associated with this mutation in the absence of antiviral **agents**. Conclusion Drug-**resistant** virus can rise to high frequencies in chronically HIV-1 infected individuals during consecutive STIs. Evolution of

resistance is likely to be more important in patients with prior suboptimal therapies, particularly when few mutations are required for **resistance**. Maximum care should be taken in designing STI protocols that minimize development of drug-**resistant** mutations that may lead to treatment failure. Thus, drug-**resistance** testing may be useful before restarting treatment during STI studies.

TI Selection of drug-**resistant** HIV-1 mutants in response to repeated structured treatment interruptions.

AB . . . repeated structured treatment interruptions (STI) is currently being evaluated in clinical trials to determine whether immune cell-mediated control of viral **replication** can be stimulated by intermittent periods of viral **replication**. The potential for selection of drug-**resistant quasi-species** remains a major concern of such a treatment strategy. Methods Plasma and peripheral blood lymphocyte (PBL) samples from 12 patients. . . . had three consecutive STIs were studied. Genotypic analysis was based on population and clonal sequencing. Drug susceptibility and their corresponding **replication** capacities were evaluated by a single-cycle growth assay. Results Consistent with a loss of phenotypic susceptibility to lamivudine, the M184V. . . . samples revealed a step-wise increase in the M184V mutation in each patient virus population over successive STIs, despite the lower **replicative** capacity associated with this mutation in the absence of antiviral **agents**. Conclusion Drug-**resistant** virus can rise to high frequencies in chronically HIV-1 infected individuals during consecutive STIs. Evolution of **resistance** is likely to be more important in patients with prior suboptimal therapies, particularly when few mutations are required for **resistance**. Maximum care should be taken in designing STI protocols that minimize development of drug-**resistant** mutations that may lead to treatment failure. Thus, drug-**resistance** testing may be useful before restarting treatment during STI studies.

IT . . .
analysis: analytical method, genetic method; single-cycle growth assay: evaluation method

IT Miscellaneous Descriptors
repeated structured treatment interruptions [repeated STIs]; viral **replication**

ORGN . . .
Primates, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae: Animal Viruses, Viruses, Microorganisms

ORGN Organism Name
HIV [human immunodeficiency virus] (Retroviridae): M184V mutation, drug-**resistant** mutants, pathogen; human (Hominidae): host

ORGN Organism Superterms
Animal Viruses; Animals; Chordates; Humans; Mammals; Microorganisms; Primates; Vertebrates; Viruses

L5 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:56933 BIOSIS
DN PREV199698629068
TI **Resistance** to antiretroviral compounds: Implications for the clinical management of HIV infection.
AU Moyle, G. J.
CS Kobler Centre, Chelsea Westminister Hosp., 369 Fulham Road, London SW10 9NH UK
SO Immunology & Infectious Diseases (Oxford), (1995) Vol. 5, No. 3, pp. 170-182.
ISSN: 0959-4957.
DT General Review
LA English
AB Given the high rates of viral **replication** at all stages of HIV infection and the frequency with which mutations occur during each **replication** cycle, it is not surprising that a drug-**resistant** virus appears under the selective pressure of

antiretroviral therapy. Evidence linking the presence of drug-**resistant quasi-species** to clinical outcome is increasing. Information on patterns of **resistance** and cross-**resistance** to the available antiretroviral **agents** should therefore be considered when deciding how to sequence and/or combine these **agents** to achieve maximal antiviral effects. Analysis of interactions between different mutations, both synergistic and antagonistic, may also be of use when selecting optimum treatment regimens in clinical practice.

TI **Resistance** to antiretroviral compounds: Implications for the clinical management of HIV infection.

AB Given the high rates of viral **replication** at all stages of HIV infection and the frequency with which mutations occur during each **replication** cycle, it is not surprising that a drug-**resistant** virus appears under the selective pressure of antiretroviral therapy. Evidence linking the presence of drug-**resistant quasi-species** to clinical outcome is increasing. Information on patterns of **resistance** and cross-**resistance** to the available antiretroviral **agents** should therefore be considered when deciding how to sequence and/or combine these **agents** to achieve maximal antiviral effects. Analysis of interactions between different mutations, both synergistic and antagonistic, may also be of use. . .

IT Miscellaneous Descriptors
ANTAGONISTIC INTERACTION; ANTIRETROVIRAL **AGENTS**; COMBINATION THERAPY; CROSS-**RESISTANCE**; DRUG-DRUG INTERACTION; MUTATION; SYNERGISTIC INTERACTION; VIRAL **REPLICATION**

L5 ANSWER 8 OF 10 MEDLINE on STN
AN 2003180869 MEDLINE
DN 22585562 PubMed ID: 12700450
TI Theoretical rationale for the use of sequential single-drug antiretroviral therapy for treatment of HIV infection.
AU Phillips Andrew N; Youle Michael S; Lampe Fiona; Johnson Margaret; Sabin Caroline A; Lepri Alessandro Cozzi; Loveday Clive
CS Royal Free Centre for HIV Medicine and Department of Primary Care and Population Sciences, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK.. a.phillips@pcps.ucl.ac.uk
SO AIDS, (2003 May 2) 17 (7) 1009-16.
Journal code: 8710219. ISSN: 0269-9370.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 200306
ED Entered STN: 20030418
Last Updated on STN: 20030624
Entered Medline: 20030623
AB BACKGROUND: Subpopulations of HIV with mutations associated with **resistance** to antiretroviral drugs often have reduced **replicative** capacity, so virus with **resistance** mutations for all existing and new antiretroviral drugs is likely to be appreciably impaired. Issues of toxicity, quality of life and economics mean that the simultaneous use of all these drugs in combination is unrealistic. We aimed to explore the use of sequential monotherapy regimens using a mathematical model of **quasi-species** dynamics, to see if these could take advantage of the poor **replicative** capacity of highly **resistant** virus. METHODS: We assume for each of seven drugs that a single mutation is associated with the ability to **replicate** (effective reproductive ratio, R > 1) in the presence of that drug as monotherapy. Parameters included were drug efficacy, the cost of **resistance** mutations and the number of new target cells arising daily. RESULTS: The use of seven drugs in a daily/weekly sequential monotherapy cycle led to substantial viral suppression (in the

presence of all **resistant** viral subpopulations) for a wider range of parameter values than a continuous five-drug regimen. Although on any one day/week there is a viral subpopulation with R > 1 (e.g. that with **resistance** only to the current drug), this subpopulation does not have time to grow sufficiently during the short period when that drug is being taken. CONCLUSION: These results provide a rationale for trials of sequential regimens, using as wide a number of drugs with different **resistance**-associated mutations as possible, as a potential '**resistance**-proof' strategy for achieving significant viral load suppression.

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CT Check Tags: Human; Support, Non-U.S. Gov't
***Anti-HIV Agents: TU, therapeutic use**
Drug Resistance, Multiple: GE, genetics
Drug Resistance, Viral: GE, genetics
*HIV Infections: DT, drug therapy
HIV Infections: GE, genetics
Models, Biological
Mutation: GE, genetics

CN 0 (Anti-HIV **Agents**)

L5 ANSWER 9 OF 10 MEDLINE on STN
AN 2000388374 MEDLINE
DN 20360300 PubMed ID: 10901843
TI [Variability and development of viral populations: assessment and implications].
Variabilite et evolution des populations virales: bilan et implications.
AU Baranowski E; Ruiz-Jarabo C M; Escarmis C; Domingo E
CS Centro de Biologia Molecular Severo Ochoa (CSIC-UAM), Universidad Autonoma de Madrid, Cantoblanco, Espana.. edomingo@cbm.uam.es
SO MEDECINE TROPICALE, (1999) 59 (4 Pt 2) 430-4. Ref: 49
Journal code: 8710146. ISSN: 0025-682X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals; AIDS
EM 200008
ED Entered STN: 20000818

Last Updated on STN: 20000818
Entered Medline: 20000809

AB RNA virus populations consist of complex distributions of closely related but not identical genomes known as viral **quasi-species** . The **quasi-species** concept describes the dynamics of these genomes subjected to a continuous process of variation, competition, and selection. **Quasi-species** dynamics has broad implications not only in the understanding of the molecular mechanisms underlying adaptation of RNA viruses but also in the design of strategies for control and prevention of viral disease. Viral load and genetic heterogeneity have a determinant influence on the adaptation of RNA virus to their environment. Vaccines designed to control diseases caused by highly variable viruses must contain several B and T epitopes to provide an ample and diversified immune response. Similarly, antiviral drugs should be used in combination therapy to minimize selection of **resistant** viruses. The theoretical model of **quasi-species** has opened the way for new antiviral therapies based on augmentation of the mutation rate during **replication** of viral RNA. Finally the **quasi-species** concept provides the basis for defining the selective factors that could influence the evolution of RNA virus and promote the emergence or reemergence of viral diseases.

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CT Check Tags: Human; Support, Non-U.S. Gov't
Antibiosis
Antiviral Agents: TU, therapeutic use
English Abstract
Epitopes: IM, immunology
Genome, Viral
Molecular Biology
Mutation: GE, genetics
RNA Virus Infections:. . . GE, genetics
RNA Viruses: IM, immunology
*RNA Viruses: PH, physiology
Selection (Genetics)
Variation (Genetics)
Viral Load
Viral Vaccines: IM, immunology
Virus Replication: GE, genetics

CN 0 (Antiviral **Agents**); 0 (Epitopes); 0 (Viral Vaccines)

L5 ANSWER 10 OF 10 MEDLINE on STN
AN 2000190254 MEDLINE
DN 20190254 PubMed ID: 10726055
TI Molecular tools for the treatment of hepatitis C.
AU Pawlotsky J M; Gretch D R
CS Department of Bacteriology and Virology, Hopital Henri Mondor, Universite Paris XII, Creteil, France.
SO ANTIVIRAL THERAPY, (1998) 3 (Suppl 3) 45-55. Ref: 77
Journal code: 9815705. ISSN: 1359-6535.

CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 200004
ED Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000426
AB The treatment of chronic hepatitis C is aimed at eliminating viral **replication** in order to prevent further evolution towards cirrhosis and hepatocellular carcinoma. Virological parameters include hepatitis C virus (HCV) genotype, qualitative viraemia, quantitative viral load and the characteristics of HCV **quasi-species** heterogeneity. These parameters can be used to predict and monitor the response to therapy, in order to help clinicians to tailor treatment of chronic hepatitis C and to better understand the molecular mechanisms underlying HCV **resistance** to antiviral drugs. Current knowledge on these various issues is reviewed in the present article.
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CT Check Tags: Human
Antiviral Agents: TU, therapeutic use
Biological Markers: AN, analysis
Drug Resistance, Microbial: GE, genetics
Genetic Techniques
Genotype
Hepacivirus: DE, drug effects
Hepacivirus: GE, genetics
*Hepacivirus: IP, isolation & purification
. . . pharmacology
Interferon-alpha: TU, therapeutic use
RNA, Viral: AN, analysis
Ribavirin: TU, therapeutic use
Time Factors
Variation (Genetics)
Viral Load
Viremia
Virus Replication
CN 0 (Antiviral **Agents**); 0 (Biological Markers); 0 (Interferon-alpha); 0 (RNA, Viral)

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STN. 10/032987

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L4 ANSWER 1 OF 20 MEDLINE on STN DUPLICATE 1
AN 2003180869 MEDLINE
DN 22585562 PubMed ID: 12700450
TI Theoretical rationale for the use of sequential single-drug antiretroviral therapy for treatment of HIV infection.
AU Phillips Andrew N; Youle Michael S; Lampe Fiona; Johnson Margaret; Sabin Caroline A; Lepri Alessandro Cozzi; Loveday Clive
CS Royal Free Centre for HIV Medicine and Department of Primary Care and Population Sciences, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK.. a.phillips@pcps.ucl.ac.uk
SO AIDS, (2003 May 2) 17 (7) 1009-16.
Journal code: 8710219. ISSN: 0269-9370.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 200306
ED Entered STN: 20030418
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AB BACKGROUND: Subpopulations of HIV with mutations associated with **resistance** to antiretroviral drugs often have reduced replicative capacity, so virus with **resistance** mutations for all existing and new antiretroviral drugs is likely to be appreciably impaired. Issues of toxicity, quality of life and economics mean that the simultaneous use of all these drugs in combination is unrealistic. We aimed to explore the use of sequential monotherapy regimens using a mathematical model of **quasi-species** dynamics, to see if these could take advantage of the poor replicative capacity of highly **resistant** virus. METHODS: We assume for each of seven drugs that a single mutation is associated with the ability to replicate (effective reproductive ratio, R > 1) in the presence of that drug as monotherapy. Parameters included were drug efficacy, the cost of **resistance** mutations and the number of new target cells arising daily. RESULTS: The use of seven drugs in a daily/weekly sequential monotherapy cycle led to substantial viral suppression (in the presence of all **resistant** viral subpopulations) for a wider range of parameter values than a continuous five-drug regimen. Although on any one day/week there is a viral subpopulation with R > 1 (e.g. that with **resistance** only to the current drug), this subpopulation does not have time to grow sufficiently during the short period when that drug is being taken. CONCLUSION: These results provide a rationale for trials of sequential regimens, using as wide a number of drugs with different **resistance**-associated mutations as possible, as a potential '**resistance**-proof' strategy for achieving significant viral load suppression.
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***Anti-HIV Agents: TU, therapeutic use**
Drug Resistance, Multiple: GE, genetics
Drug Resistance, Viral: GE, genetics
*HIV Infections: DT, drug therapy
HIV Infections: GE, genetics
Models, Biological
Mutation: GE, genetics

CN 0 (Anti-HIV **Agents**)

L4 ANSWER 2 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:487349 BIOSIS
DN PREV200200487349
TI Process and **agent** for instabilizing viral **quasi-species**-distributions avoiding **resistance** phenomena.
AU Eigen, Manfred (1); Schwienhorst, Andreas; Biebricher, Christof; Lindemann, Bjorn; Domingo, Esteban; Holland, John; Henco, Karsten
CS (1) Gottingen Germany
ASSIGNEE: Evotec BioSystems AG, Hamburg, Germany
PI US 6423516 July 23, 2002
SO Official Gazette of the United States Patent and Trademark Office Patents, (July 23, 2002) Vol. 1260, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133.
DT Patent
LA English
AB A process for instabilizing viral **quasi-species**-distributions under avoidance of **resistance** phenomena by replication of the nucleic acids of the viruses present in the **quasi-species**-distribution by of a defective replication system, a) whereby the defective replication system has a rate of misincorporation for nucleotides above the rate of misincorporation of the viral wild-type-replication system and, whereby the viruses are replicated by the replication system having the higher rate of misincorporation at least as effectively as it is done by the replication system of the wild-type virus, b) and/or negative influence of the replication of the consensus-sequence (nucleic acid sequence of the wild-type virus) in relation to other replicatable nucleic acids.
TI Process and **agent** for instabilizing viral **quasi-species**-distributions avoiding **resistance** phenomena.
AB A process for instabilizing viral **quasi-species**-distributions under avoidance of **resistance** phenomena by replication of the nucleic acids of the viruses present in the **quasi-species**-distribution by of a defective replication system, a) whereby the defective replication system has a rate of misincorporation for nucleotides above. . .
IT Miscellaneous Descriptors
defective replication system: nucleotide misincorporation rate; **resistance** phenomena avoidance; viral **quasi-species**-distributions: instabilizing process

L4 ANSWER 3 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
AN 2002:298017 BIOSIS
DN PREV200200298017
TI Selection of drug-**resistant** HIV-1 mutants in response to repeated structured treatment interruptions.

AU Martinez-Picado, Javier (1); Morales-Lopetegi, Kristina; Wrin, Terri; Prado, Julia G.; Frost, Simon D. W.; Petropoulos, Christos J.; Clotet, Bonaventura; Ruiz, Lidia

CS (1) Hospital Germans Trias i Pujol, IrsiCaixa Foundation, Ctra. de Canyet s/n, 08916, Badalona: javiermp@ns.hugtip.scs.es Spain

SO AIDS (Hagerstown), (12 April, 2002) Vol. 16, No. 6, pp. 895-899. http://www.aidsonline.com/. print.
ISSN: 0269-9370.

DT Article

LA English

AB Background A new HIV-1 treatment strategy based on repeated structured treatment interruptions (STI) is currently being evaluated in clinical trials to determine whether immune cell-mediated control of viral replication can be stimulated by intermittent periods of viral replication. The potential for selection of drug-**resistant quasi-species** remains a major concern of such a treatment strategy. Methods Plasma and peripheral blood lymphocyte (PBL) samples from 12 patients who had three consecutive STIs were studied. Genotypic analysis was based on population and clonal sequencing. Drug susceptibility and their corresponding replication capacities were evaluated by a single-cycle growth assay. Results Consistent with a loss of phenotypic susceptibility to lamivudine, the M184V mutation was detected by genotypic analysis (direct and clonal sequencing) in plasma samples collected from two patients at the end of the second or third STI. Longitudinal analysis of patient samples revealed a step-wise increase in the M184V mutation in each patient virus population over successive STIs, despite the lower replicative capacity associated with this mutation in the absence of antiviral **agents**. Conclusion Drug-**resistant** virus can rise to high frequencies in chronically HIV-1 infected individuals during consecutive STIs. Evolution of **resistance** is likely to be more important in patients with prior suboptimal therapies, particularly when few mutations are required for **resistance**. Maximum care should be taken in designing STI protocols that minimize development of drug-**resistant** mutations that may lead to treatment failure. Thus, drug-**resistance** testing may be useful before restarting treatment during STI studies.

TI Selection of drug-**resistant** HIV-1 mutants in response to repeated structured treatment interruptions.

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ORGN . . .
Primates, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae: Animal Viruses, Viruses, Microorganisms

ORGN Organism Name
HIV [human immunodeficiency virus] (Retroviridae): M184V mutation, drug-**resistant** mutants, pathogen; human (Hominidae): host

ORGN Organism Superterms
Animal Viruses; Animals; Chordates; Humans; Mammals; Microorganisms; Primates; Vertebrates; Viruses

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:223197 CAPLUS
DN 137:4861
TI Emergence of autologous neutralization-**resistant** variants from preexisting human immunodeficiency virus (HIV) **quasi species** during virus rebound in HIV type 1-infected patients undergoing highly active antiretroviral therapy
AU Wang, Feng-Xiang; Kimura, Tetsuya; Nishihara, Kumiko; Yoshimura, Kazuhisa; Koito, Atsushi; Matsushita, Shuzo
CS Division of Clinical Retrovirology and Infectious Diseases, Center for AIDS Research, Graduate School of Science and Technology, Kumamoto University, Kumamoto, 860-0811, Japan
SO Journal of Infectious Diseases (2002), 185(5), 608-617
CODEN: JIDIAQ; ISSN: 0022-1899
PB University of Chicago Press
DT Journal
LA English
AB The role of neutralizing antibodies (NAbs) during virus rebound in human immunodeficiency virus type 1 (HIV-1)-infected patients undergoing highly active anti-retroviral therapy is poorly understood. Three patients in this study had NAbs to preexisting autologous HIV-1 and an episode of virus rebound after a prolonged period of virus suppression. To investigate the influence of NAbs on virus evolution, envelope genotypes of pre-existing and rebound viruses were examd. Phylogenetic anal. of env (V1-V5) sequences indicated that rebound viruses had evolved from or pre-existed in baseline populations. By use of envelope pseudotype viruses, rebound viruses were significantly **resistant** to neutralization by autologous antibody in all 3 patients, indicating that rebound viruses were selected by NAbs. The site responsible for conferring neutralization **resistance** against autologous antibody was identified in the upstream C3 region in 2 of 3 patients.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Emergence of autologous neutralization-**resistant** variants from preexisting human immunodeficiency virus (HIV) **quasi species** during virus rebound in HIV type 1-infected patients undergoing highly active antiretroviral therapy
AB The role of neutralizing antibodies (NAbs) during virus rebound in human immunodeficiency virus type 1 (HIV-1)-infected patients undergoing highly active anti-retroviral therapy is poorly understood. Three patients in this study had NAbs to preexisting autologous HIV-1 and an episode of virus rebound after a prolonged period of virus suppression. To investigate the influence of NAbs on virus evolution, envelope genotypes of pre-existing and rebound viruses were examd. Phylogenetic anal. of env (V1-V5) sequences indicated that rebound viruses had evolved from or pre-existed in baseline populations. By use of envelope pseudotype viruses, rebound viruses were significantly **resistant** to neutralization by autologous antibody in all 3 patients, indicating that rebound viruses were selected by NAbs. The site responsible for conferring neutralization **resistance** against autologous antibody was identified in the upstream C3 region in 2 of 3 patients.
ST neutralizing antibody **resistance** immunodeficiency virus envelope protein
IT Anti-AIDS **agents**
(HAART; antibodies select for neutralization-**resistant** variants of human immunodeficiency virus during rebound from)
IT Antigenic variation
Human
Human immunodeficiency virus 1
(antibodies select for neutralization-**resistant** variants of human immunodeficiency virus during rebound from HAART)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(env; antibodies select for neutralization-**resistant** variants of human immunodeficiency virus during rebound from HAART)

IT Protein sequences
Viral RNA sequences
(for envelope protein loop regions of neutralization-**resistant** HIV-1)

IT Envelope proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(gene env; antibodies select for neutralization-**resistant** variants of human immunodeficiency virus during rebound from HAART)

IT Antibodies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(neutralizing; antibodies select for neutralization-**resistant** variants of human immunodeficiency virus during rebound from HAART)

IT 330622-74-7, GenBank AB059279 330622-75-8, GenBank AB059280
330622-76-9, GenBank AB059281 330622-77-0, GenBank AB059282
330622-78-1, GenBank AB059283 330622-79-2, GenBank AB059284
330622-80-5, GenBank AB059285 330622-81-6, GenBank AB059286
330622-82-7, GenBank AB059287 330622-83-8, GenBank AB059288
330622-84-9, GenBank AB059289 330622-85-0, GenBank AB059290
330622-86-1, GenBank AB059291 330622-87-2, GenBank AB059292
330622-88-3, GenBank AB059293 330622-89-4, GenBank AB059294
330622-90-7, GenBank AB059296 330622-91-8, GenBank AB059297
330622-92-9, GenBank AB059298 330622-93-0, GenBank AB059299
330622-94-1, GenBank AB059300 330622-95-2, GenBank AB059301
330622-96-3, GenBank AB059302 330622-97-4, GenBank AB059303
330622-98-5, GenBank AB059304 330622-99-6, GenBank AB059305
330623-00-2, GenBank AB059307 330623-01-3, GenBank AB059308
330623-02-4, GenBank AB059309 330623-03-5, GenBank AB059310
330623-04-6, GenBank AB059311 330623-05-7, GenBank AB059312
330623-06-8, GenBank AB059313 330623-07-9, GenBank AB059314
330623-08-0, GenBank AB059315 330623-09-1, GenBank AB059316
330623-10-4, GenBank AB059317 330623-11-5, GenBank AB059318
330623-12-6, GenBank AB059319 330623-13-7, GenBank AB059320
330623-14-8, GenBank AB059321 330623-15-9, GenBank AB059322
330623-16-0, GenBank AB059323 330623-17-1, GenBank AB059324
330623-18-2, GenBank AB059325 330623-19-3, GenBank AB059326
382531-25-1, GenBank AB059295 382531-26-2, GenBank AB059306
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; antibodies select for neutralization-**resistant** variants of human immunodeficiency virus during rebound from HAART)

L4 ANSWER 5 OF 20 MEDLINE on STN
AN 2002094073 MEDLINE
DN 21681314 PubMed ID: 11807683
TI Prolonged excretion of amantadine-**resistant** influenza a virus **quasi species** after cessation of antiviral therapy in an immunocompromised patient.
AU Boivin Guy; Goyette Nathalie; Bernatchez Harold
CS Research Center in Infectious Diseases, Centre Hospitalier de l'Universite Laval, Sainte-Foy, Quebec, Canada.. Guy.Boivin@crchul.ulaval.ca
SO CLINICAL INFECTIOUS DISEASES, (2002 Mar 1) 34 (5) E23-5.
Journal code: 9203213. ISSN: 1537-6591.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020202
Last Updated on STN: 20030105
Entered Medline: 20020228

AB Phenotypic and molecular studies were conducted to characterize multiple influenza A isolates recovered from an immunocompromised patient who died of viral and fungal pneumonitis. The recovery of amantadine-**resistant** isolates was correlated with the detection of 2 drug-**resistant** M2 variants (codons 27 and 31) in combination with a wild-type virus. The mutant viruses persisted within the viral population in variable proportions >1 month after cessation of antiviral therapy. These results confirm animal studies reported elsewhere regarding the genetic stability of influenza M2 mutants and their potential for transmission in humans.

TI Prolonged excretion of amantadine-**resistant** influenza a virus **quasi species** after cessation of antiviral therapy in an immunocompromised patient.

AB . . . characterize multiple influenza A isolates recovered from an immunocompromised patient who died of viral and fungal pneumonitis. The recovery of amantadine-**resistant** isolates was correlated with the detection of 2 drug-**resistant** M2 variants (codons 27 and 31) in combination with a wild-type virus. The mutant viruses persisted within the viral population. . .

CT Check Tags: Case Report; Human; Male
*Amantadine: PD, pharmacology
Amantadine: TU, therapeutic use
***Antiviral Agents: PD, pharmacology**
Antiviral Agents: TU, therapeutic use
***Drug Resistance, Microbial: GE, genetics**
Genotype
Immunocompromised Host
Influenza A virus: DE, drug effects
*Influenza A virus: GE, genetics
Middle Age

. . .

CN 0 (Antiviral **Agents**)

L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3
AN 2002:17201 CAPLUS
DN 137:119080
TI In vivo HIV-1 compartmentalisation: drug **resistance**-associated mutation distribution
AU Devereux, Helen L.; Burke, Andy; Lee, Christine A.; Johnson, Margaret A.
CS Department of Retrovirology, Royal Free and University College Medical School, London, UK
SO Journal of Medical Virology (2002), 66(1), 8-12
CODEN: JMVIDB; ISSN: 0146-6615
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Four patients who had received highly active anti-retroviral therapy (HAART), and had postmortem samples stored, were tested for genotypic **resistance** using consensus sequencing. One patient was further investigated using single-copy sequencing. Patients 1, 3, and 4 showed a relatively uniform distribution of **resistance**-assocd. mutations, with only a small no. (one to three) of protease mutations detectable. Patient 2 had a no. of detectable mutations (four to eight, depending on the tissue) with similar distributions between the tissues. The exception was viruses detected in the esophagus, which were more diverse. Plasma was a moderately representative tissue of the viruses circulating in these individuals. However, some mutations detectable in some tissues were not seen in plasma (e.g., M46I and D30N in the protease). Single-copy sequencing revealed a wide distribution of **quasi-species** and a no. of defective viruses in the proviral DNA and RNA. This study supports the concept that a wide variety of **quasi-species** circulate in each individual and that there may be viruses evolving independently in different body compartments.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI In vivo HIV-1 compartmentalisation: drug **resistance**-associated mutation distribution

AB Four patients who had received highly active anti-retroviral therapy (HAART), and had postmortem samples stored, were tested for genotypic **resistance** using consensus sequencing. One patient was further investigated using single-copy sequencing. Patients 1, 3, and 4 showed a relatively uniform distribution of **resistance**-assocd. mutations, with only a small no. (one to three) of protease mutations detectable. Patient 2 had a no. of detectable mutations (four to eight, depending on the tissue) with similar distributions between the tissues. The exception was viruses detected in the esophagus, which were more diverse. Plasma was a moderately representative tissue of the viruses circulating in these individuals. However, some mutations detectable in some tissues were not seen in plasma (e.g., M46I and D30N in the protease). Single-copy sequencing revealed a wide distribution of **quasi-species** and a no. of defective viruses in the proviral DNA and RNA. This study supports the concept that a wide variety of **quasi-species** circulate in each individual and that there may be viruses evolving independently in different body compartments.

ST HIV1 virus mutation organ compartmentalization antiviral drug **resistance**

IT Anti-AIDS **agents**
(HAART (highly active anti-retroviral therapy); in vivo HIV-1 compartmentalization and drug **resistance**-assocd. mutation distribution)

IT Drug **resistance**
(antiviral; in vivo HIV-1 compartmentalization and drug **resistance**-assocd. mutation distribution)

IT Animal tissue
Organ, animal
(distribution; in vivo HIV-1 compartmentalization and drug **resistance**-assocd. mutation distribution)

IT Human
Human immunodeficiency virus 1
Mutation
(in vivo HIV-1 compartmentalization and drug **resistance** -assocd. mutation distribution)

IT Antiviral **agents**
(**resistance** to; in vivo HIV-1 compartmentalization and drug **resistance**-assocd. mutation distribution)

IT 9068-38-6, Reverse transcriptase 144114-21-6, HIV-1 proteinase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mutation, tissue distribution; in vivo HIV-1 compartmentalization and drug **resistance**-assocd. mutation distribution)

L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4

AN 2001:490145 CAPLUS

DN 135:282733

TI Changes in human immunodeficiency virus type 1 populations after treatment interruption in patients failing antiretroviral therapy

AU Hance, Allan J.; Lemiale, Virginie; Izopet, Jacques; Lecossier, Denise; Joly, Veronique; Massip, Patrice; Mammano, Fabrizio; Descamps, Diane; Brun-Vezinet, Francoise; Clavel, Francois

CS INSERM U552, Hopital Bichat-Claude Bernard, Paris, 75018, Fr.

SO Journal of Virology (2001), 75(14), 6410-6417
CODEN: JOVIAM; ISSN: 0022-538X

PB American Society for Microbiology

DT Journal

LA English

AB Mutations in human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and protease that confer **resistance** to antiretroviral **agents** are usually accompanied by a redn. in the

viral replicative capacity under drug-free conditions. Consequently, when antiretroviral treatment is interrupted in HIV-1-infected patients harboring drug-**resistant** virus, **resistant quasi-species** appear to be most often replaced within several weeks by wild-type virus. Using a real-time PCR-based technique for the selective quantification of **resistant** viral sequences in plasma, we have studied the kinetics of the switch from mutant to wild-type virus and evaluated the extent to which minority populations of **resistant** viruses not detected by genotyping persist in these individuals. Among 12 patients with viruses expressing the V82A or L90M **resistance** mutation who had undergone a 3-mo interruption of therapy and for whom conventional genotyping had revealed an apparent total reconversion to wild-type virus, minority populations expressing these mutations, representing 0.1 to 21% of total virus, were still detectable in 9 cases. Kinetic studies demonstrated that viruses expressing **resistance** mutations could be detected for >5 mo after the discontinuation of treatment in some patients. Most of the minority **resistant** genomes detected more than 3 mo after the interruption of therapy carried only part of the mutations present in the **resistant** viruses prior to treatment interruption and appeared to result from the emergence of existing strains selected at earlier stages in the development of drug **resistance**. Thus, following the interruption of treatment, viral populations contg. **resistance** mutations can persist for several months after the time when conventional genotyping techniques detect only wild-type virus. These populations include viral strains with only some of the **resistance** mutations initially present, strains that presumably express better fitness under drug-free conditions.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Mutations in human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and protease that confer **resistance** to antiretroviral **agents** are usually accompanied by a redn. in the viral replicative capacity under drug-free conditions. Consequently, when antiretroviral treatment is interrupted in HIV-1-infected patients harboring drug-**resistant** virus, **resistant quasi-species** appear to be most often replaced within several weeks by wild-type virus. Using a real-time PCR-based technique for the selective quantification of **resistant** viral sequences in plasma, we have studied the kinetics of the switch from mutant to wild-type virus and evaluated the extent to which minority populations of **resistant** viruses not detected by genotyping persist in these individuals. Among 12 patients with viruses expressing the V82A or L90M **resistance** mutation who had undergone a 3-mo interruption of therapy and for whom conventional genotyping had revealed an apparent total reconversion to wild-type virus, minority populations expressing these mutations, representing 0.1 to 21% of total virus, were still detectable in 9 cases. Kinetic studies demonstrated that viruses expressing **resistance** mutations could be detected for >5 mo after the discontinuation of treatment in some patients. Most of the minority **resistant** genomes detected more than 3 mo after the interruption of therapy carried only part of the mutations present in the **resistant** viruses prior to treatment interruption and appeared to result from the emergence of existing strains selected at earlier stages in the development of drug **resistance**. Thus, following the interruption of treatment, viral populations contg. **resistance** mutations can persist for several months after the time when conventional genotyping techniques detect only wild-type virus. These populations include viral strains with only some of the **resistance** mutations initially present, strains that presumably express better fitness under drug-free conditions.

ST antiretroviral HIV antiAIDS antiviral **resistance** genotype

IT Drug **resistance**
(antiviral; changes in HIV-1 populations after treatment interruption

in humans failing antiretroviral therapy)
IT Anti-AIDS **agents**
Genotypes
Genotyping (method)
Human immunodeficiency virus 1
Mutation
(changes in HIV-1 populations after treatment interruption in humans failing antiretroviral therapy)
IT Antiviral **agents**
(**resistance** to; changes in HIV-1 populations after treatment interruption in humans failing antiretroviral therapy)

L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 5
AN 2001:824300 CAPLUS
DN 136:100731
TI Effect of HCV viral dynamics on treatment design: Lessons learned from HIV
AU Bain, Vincent G.
CS Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, AB, Can.
SO American Journal of Gastroenterology (2001), 96(10), 2818-2828
CODEN: AJGAAR; ISSN: 0002-9270
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A review. Viral load measurements provide an indication of viral replication, and thereby serve as a valuable tool to guide the initiation of therapy and subsequent changes. Plasma human immunodeficiency viral load strongly predicts the rate of decrease in CD4+ lymphocyte count, and progression to AIDS and death. Furthermore, the efficacy of antiretroviral therapy can be assessed by monitoring changes in plasma human immunodeficiency viral load. Similarly, viral load provides valuable information about the natural history of the hepatitis C virus infection. Hepatitis C viral load can be used to predict the likelihood of response to std. interferon-.alpha. treatment and other interferon-.alpha. regimens and to monitor treatment efficacy. Increased understanding of the natural history of the hepatitis C virus infection and the nature of **resistance** to interferon-.alpha. therapy suggests that effective treatment regimens must maintain serum levels of interferon-.alpha.. Ideally, interferon-.alpha. serum levels should provide const. pressure on the virus and should prevent viral rebound, thereby avoiding continued viral replication and minimizing the potential for emergence of **resistant quasi-species**.
Current regimens designed to address these points include early aggressive intervention, combination drug regimens, prolonged maintenance, and novel interferons. By enabling the design and rapid assessment of new treatment regimens, viral load measurement will revolutionize the clin. management of the hepatitis C virus infection, as it has the HIV.
RE.CNT 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review. Viral load measurements provide an indication of viral replication, and thereby serve as a valuable tool to guide the initiation of therapy and subsequent changes. Plasma human immunodeficiency viral load strongly predicts the rate of decrease in CD4+ lymphocyte count, and progression to AIDS and death. Furthermore, the efficacy of antiretroviral therapy can be assessed by monitoring changes in plasma human immunodeficiency viral load. Similarly, viral load provides valuable information about the natural history of the hepatitis C virus infection. Hepatitis C viral load can be used to predict the likelihood of response to std. interferon-.alpha. treatment and other interferon-.alpha. regimens and to monitor treatment efficacy. Increased understanding of the natural history of the hepatitis C virus infection and the nature of **resistance** to interferon-.alpha. therapy suggests that effective treatment regimens must maintain serum levels of interferon-.alpha.. Ideally, interferon-.alpha. serum levels should

provide const. pressure on the virus and should prevent viral rebound, thereby avoiding continued viral replication and minimizing the potential for emergence of **resistant quasi-species**.
Current regimens designed to address these points include early aggressive intervention, combination drug regimens, prolonged maintenance, and novel interferons. By enabling the design and rapid assessment of new treatment regimens, viral load measurement will revolutionize the clin. management of the hepatitis C virus infection, as it has the HIV.

IT Antiviral **agents**
Hepatitis C virus
Human
Human immunodeficiency virus
(effect of HCV viral dynamics on treatment design in humans using lessons learned from HIV)

L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 6
AN 2002:131107 CAPLUS
DN 137:195022
TI Development and application of a genotypic AZT **resistance** assay: Quantitative assessment of the **resistance** profile of clinical samples and the relative predictive ability of a **resistance** index
AU Kyriakides, Tassos C.; Heimer, Robert R.
CS Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT, 06516, USA
SO JAIDS, Journal of Acquired Immune Deficiency Syndromes (2001), 28(3), 211-220
CODEN: JJASFJ
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Zidovudine (AZT) **resistance** profiles of plasma samples from HIV-infected patients were detd. by a ligase chain reaction assay. AZT **resistance** levels and surrogate markers of HIV disease progression (viral load and CD4 counts) were used to compare AZT-naive and AZT-experienced patients. The ability of a "mutant/wild-type HIV-1 **quasi-species**" index to predict viral load was assessed. AZT **resistance**, evident under basal conditions in both AZT-experienced and AZT-naive patients, increased over 6 mo of treatment. The **resistance** profile of AZT-naive patients differed from that of AZT-experienced patients; viral load and CD4 counts were similar. The relative predictive ability (for subsequent viral load) of the **resistance** index was similar to or higher than that of the basal viral load or CD4 count. This assay used to detect AZT **resistance** could be adapted for use with other antiretroviral compds. The predictive ability of the proposed **resistance** index was equal to or surpassed that of viral load and CD4 count, lending further support to the use of **resistance** assays in selecting drug regimens both before and during antiretroviral therapy.
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Development and application of a genotypic AZT **resistance** assay: Quantitative assessment of the **resistance** profile of clinical samples and the relative predictive ability of a **resistance** index
AB Zidovudine (AZT) **resistance** profiles of plasma samples from HIV-infected patients were detd. by a ligase chain reaction assay. AZT **resistance** levels and surrogate markers of HIV disease progression (viral load and CD4 counts) were used to compare AZT-naive and AZT-experienced patients. The ability of a "mutant/wild-type HIV-1 **quasi-species**" index to predict viral load was assessed. AZT **resistance**, evident under basal conditions in both AZT-experienced and AZT-naive patients, increased over 6 mo of treatment. The **resistance** profile of AZT-naive patients differed from that

of AZT-experienced patients; viral load and CD4 counts were similar. The relative predictive ability (for subsequent viral load) of the **resistance** index was similar to or higher than that of the basal viral load or CD4 count. This assay used to detect AZT **resistance** could be adapted for use with other antiretroviral compds. The predictive ability of the proposed **resistance** index was equal to or surpassed that of viral load and CD4 count, lending further support to the use of **resistance** assays in selecting drug regimens both before and during antiretroviral therapy.

ST zidovudine HIV **resistance** assay; azidothymidine HIV **resistance** assay

IT Anti-AIDS **agents**
Drug **resistance**
Human
(zidovudine **resistance** assay)

IT Human immunodeficiency virus 1
(zidovudine **resistance** assay in persons infected with)

IT 30516-87-1, Zidovudine
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zidovudine **resistance** assay)

L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:681298 CAPLUS
DN 134:146162
TI The protein kinase-interacting domain in the hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon
AU Polyak, Stephen J.; Nousbaum, Jean-Baptiste; Larson, Anne M.; Cotler, Scott; Carithers, Robert L., Jr.; Gretch, David R.
CS Department of Laboratory Medicine, University of Washington, Seattle, WA, USA
SO Journal of Infectious Diseases (2000), 182(2), 397-404
CODEN: JIDIAQ; ISSN: 0022-1899
PB University of Chicago Press
DT Journal
LA English
AB The hepatitis C virus (HCV) envelope glycoprotein-2 inhibits the interferon (IFN)-induced, double-stranded RNA-activated protein kinase (PKR) via the PKR eukaryotic initiation factor-2.alpha. phosphorylation homol. domain (PePHD). The present study examd. the genetic variability of the PePHD in patients receiving IFN therapy. The PePHD from 12 HCV genotype 1 (HCV-1)-infected patients receiving daily IFN therapy was amplified by reverse-transcriptase polymerase chain reaction and analyzed by direct and clonal sequencing. The PePHD was highly conserved in 38 HCV GenBank isolates. There was no difference in pretreatment PePHD sequences isolated from IFN responders vs. nonresponders. The major PePHD **quasi-species** variant did not change after 6 wk of daily IFN therapy, and in 1 patient the major **quasi-species** variant did not change during 9 mo of observation. Sequencing of 25 pretreatment PePHD clones from 3 patients confirmed that there was extremely low sequence variability surrounding the PePHD. Thus, the PePHD is highly conserved in HCV-1-infected IFN responders and nonresponders and does not appear to evolve in response to IFN therapy.
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The hepatitis C virus (HCV) envelope glycoprotein-2 inhibits the interferon (IFN)-induced, double-stranded RNA-activated protein kinase (PKR) via the PKR eukaryotic initiation factor-2.alpha. phosphorylation homol. domain (PePHD). The present study examd. the genetic variability of the PePHD in patients receiving IFN therapy. The PePHD from 12 HCV genotype 1 (HCV-1)-infected patients receiving daily IFN therapy was amplified by reverse-transcriptase polymerase chain reaction and analyzed

by direct and clonal sequencing. The PePHD was highly conserved in 38 HCV GenBank isolates. There was no difference in pretreatment PePHD sequences isolated from IFN responders vs. nonresponders. The major PePHD **quasi-species** variant did not change after 6 wk of daily IFN therapy, and in 1 patient the major **quasi-species** variant did not change during 9 mo of observation. Sequencing of 25 pretreatment PePHD clones from 3 patients confirmed that there was extremely low sequence variability surrounding the PePHD. Thus, the PePHD is highly conserved in HCV-1-infected IFN responders and nonresponders and does not appear to evolve in response to IFN therapy.

IT Drug **resistance**
(antiviral; protein kinase-interacting domain in hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon)

IT Antiviral **agents**
(**resistance** to; protein kinase-interacting domain in hepatitis C virus envelope glycoprotein-2 gene is highly conserved in genotype 1-infected patients treated with interferon)

L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:197381 CAPLUS
DN 132:206794
TI The NS5a gene of hepatitis C virus in patients treated with interferon-.alpha.
AU McKechnie, Victoria M.; Mills, Peter R.; McCruden, Elizabeth A. B.
CS Division of Virology, University of Glasgow, Glasgow, G11 5JR, UK
SO Journal of Medical Virology (2000), 60(4), 367-378
CODEN: JMVIDB; ISSN: 0146-6615
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Patients infected with hepatitis C virus (HCV) genotype 3 have a better response to interferon-.alpha. (IFN-.alpha.) therapy than those infected with genotype 1. There are extensive sequence differences between genotypes in the 3' half of the NS5a gene. An assocn. between IFN-.alpha. response and the interferon sensitivity-detg. region (ISDR) (amino acids 2209-2248) of HCV genotype 1b has been described [Enomoto et al. (1996) New England Journal of Medicine 334: 771-776]. A prospective study was conducted to det. whether the derived NS5A amino acid sequence or **quasi-species** diversity could predict response to IFN-.alpha. therapy. Serum samples were obtained before, during, and after treatment from 35 IFN-.alpha.-treated patients chronically infected with HCV (eight with type1b, 13 with type 1a, and 14 with type 3a). Nucleotide sequences were detd., and amino acid sequences corresponding to residues 2178-2390 of the polyprotein were derived. **Quasi-species** complexity was analyzed by amplification of the ISDR region (2270-2403), followed by single-stranded conformation polymorphism (SSCP). No amino acid sequence that could be used to predict response to treatment was found, and there was no selection of specific amino acid residues during treatment. A striking lack of variability was seen in HCV genotype 3a, but the small degree of variation could suggest an effect on response. SSCP showed that variation in the predominant NS5a sequence occurred in the presence and absence of therapeutically administered IFN-.alpha.. HCV **quasi-species** diversity pretreatment did not predict IFN-.alpha. treatment outcome. The conclusion of the study is that the amino acid sequence of NS5a cannot be used to predict the efficacy of treatment with IFN-.alpha. in HCV-infected patients in Scotland. No evidence was found to support the selection of IFN-.alpha.-**resistant** strains in the NS5a gene.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Patients infected with hepatitis C virus (HCV) genotype 3 have a better response to interferon-.alpha. (IFN-.alpha.) therapy than those infected with genotype 1. There are extensive sequence differences between

genotypes in the 3' half of the NS5a gene. An assocn. between IFN-.alpha. response and the interferon sensitivity-detg. region (ISDR) (amino acids 2209-2248) of HCV genotype 1b has been described [Enomoto et al. (1996) New England Journal of Medicine 334: 771-776]. A prospective study was conducted to det. whether the derived NS5A amino acid sequence or **quasi-species** diversity could predict response to IFN-.alpha. therapy. Serum samples were obtained before, during, and after treatment from 35 IFN-.alpha.-treated patients chronically infected with HCV (eight with type1b, 13 with type 1a, and 14 with type 3a). Nucleotide sequences were detd., and amino acid sequences corresponding to residues 2178-2390 of the polyprotein were derived. **Quasi-species** complexity was analyzed by amplification of the ISDR region (2270-2403), followed by single-stranded conformation polymorphism (SSCP). No amino acid sequence that could be used to predict response to treatment was found, and there was no selection of specific amino acid residues during treatment. A striking lack of variability was seen in HCV genotype 3a, but the small degree of variation could suggest an effect on response. SSCP showed that variation in the predominant NS5a sequence occurred in the presence and absence of therapeutically administered IFN-.alpha.. HCV **quasi-species** diversity pretreatment did not predict IFN-.alpha. treatment outcome. The conclusion of the study is that the amino acid sequence of NS5a cannot be used to predict the efficacy of treatment with IFN-.alpha. in HCV-infected patients in Scotland. No evidence was found to support the selection of IFN-.alpha.-**resistant** strains in the NS5a gene.

IT Antiviral **agents**
Hepatitis C virus
(NS5a gene of hepatitis C virus in patients treated with interferon-.alpha.)

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 7
AN 2000:588357 CAPLUS
DN 134:36705
TI Analysis of env sequence evolution in human immunodeficiency virus-infected patients receiving therapy with nonnucleoside reverse-transcriptase inhibitors
AU Dykes, C.; Mootsikapun, P.; Dexter, A.; Berrios, L.; Chiulli, M.; Reichman, R. C.; Demeter, L. M.
CS Infectious Diseases Unit, University of Rochester School of Medicine and Dentistry, Rochester, NY, 14642, USA
SO Journal of Infectious Diseases (2000), 182(1), 316-320
CODEN: JIDIAQ; ISSN: 0022-1899
PB University of Chicago Press
DT Journal
LA English
AB Nonnucleoside reverse-transcriptase inhibitors (NNRTIs) can rapidly select for drug-**resistant** human immunodeficiency virus type 1 (HIV-1) variants, although their effect on HIV-1 **quasi-species** diversity is unknown. To det. if changes in env gene diversification occur with NNRTI therapy, the authors used the heteroduplex tracking assay (HTA) to study HIV-1 env sequence diversity in 2 groups of patients: those who were on no therapy or were on chronic antiretroviral therapy and those who had just initiated NNRTIs. 49 Paired samples from 46 patients were analyzed. 14 Of 32 paired samples from the NNRTI group and 9 of 17 paired samples from the control group had HTA changes. There was no correlation between HTA change and sampling time interval, baseline virus load, change in virus load, or development of NNRTI **resistance**. Thus, the authors found no correlation of NNRTI therapy with changes in env HTA patterns, suggesting that these treatments had little short-term impact on HIV-1 **quasi-species** diversity.
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Nonnucleoside reverse-transcriptase inhibitors (NNRTIs) can rapidly select for drug-**resistant** human immunodeficiency virus type 1 (HIV-1)

variants, although their effect on HIV-1 **quasi-species** diversity is unknown. To det. if changes in env gene diversification occur with NNRTI therapy, the authors used the heteroduplex tracking assay (HTA) to study HIV-1 env sequence diversity in 2 groups of patients: those who were on no therapy or were on chronic antiretroviral therapy and those who had just initiated NNRTIs. 49 Paired samples from 46 patients were analyzed. 14 Of 32 paired samples from the NNRTI group and 9 of 17 paired samples from the control group had HTA changes. There was no correlation between HTA change and sampling time interval, baseline virus load, change in virus load, or development of NNRTI **resistance**. Thus, the authors found no correlation of NNRTI therapy with changes in env HTA patterns, suggesting that these treatments had little short-term impact on HIV-1 **quasi-species** diversity.

ST HIV gene env sequence antiAIDS **resistance**

IT Anti-AIDS **agents**
DNA sequences
Drug **resistance**
Human immunodeficiency virus 1
Mutation
(anal. of env sequence evolution in HIV-infected patients receiving nonnucleoside reverse-transcriptase inhibitors)

L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 8
AN 2000:298864 CAPLUS
DN 133:308746
TI Physiopathology and treatment of acquired immunodeficiency syndrome
AU Soto Ramirez, Luis Enrique
CS Departamento de Infectologia. Instituto Nacional de Nutricion Salvador Zubiran, Mex.
SO Revista de Investigacion Clinica (2000), 52(1), 60-71
CODEN: RICLAG; ISSN: 0034-8376
PB Instituto Nacional de la Nutricion Salvador Zubiran
DT Journal; General Review
LA Spanish
AB A review with 65 refs. The last pandemic of the century, that of AIDS caused by the human immunodeficiency virus (HIV), continues to advance with gigantic steps at about 18,000 new infections per day worldwide. In the last 4 yr, breakthroughs have been achieved and new medications have been introduced, which have impacted the progression of HIV and its disease, decreasing assocd. morbidity and mortality. During the course of infection, HIV replicates actively producing as much as 1010 genetically different virions (**quasi-species**), which relates to immune escape, higher pathogenicity, and drug **resistance**. Persistent viral replication causes T CD4+ cell destruction and immunodeficiency through several mechanisms. Currently, there are 14 approved anti-retrovirals that when used as triple regimens have been able to decrease opportunistic infections, hospitalization, and mortality rates. Unfortunately, these regimens still have many limitations, do not cure, and can only suppress the virus effectively in 50% of the treated patients. Besides, when they are inadequately used there is assocd. **resistance** development. However, indications for treatment initiation are changing continuously and heading towards a conservative approach. In the case of salvage regimens, there are only general guidelines that have not been evaluated in clin. studies. **Resistance** assays have great limitations and their use is very specific. All these factors have made the anti-retroviral therapy a very complicated issue.
RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review with 65 refs. The last pandemic of the century, that of AIDS caused by the human immunodeficiency virus (HIV), continues to advance with gigantic steps at about 18,000 new infections per day worldwide. In the last 4 yr, breakthroughs have been achieved and new medications have been introduced, which have impacted the progression of HIV and its

disease, decreasing assocd. morbidity and mortality. During the course of infection, HIV replicates actively producing as much as 1010 genetically different virions (**quasi-species**), which relates to immune escape, higher pathogenicity, and drug **resistance**. Persistent viral replication causes T CD4+ cell destruction and immunodeficiency through several mechanisms. Currently, there are 14 approved anti-retrovirals that when used as triple regimens have been able to decrease opportunistic infections, hospitalization, and mortality rates. Unfortunately, these regimens still have many limitations, do not cure, and can only suppress the virus effectively in 50% of the treated patients. Besides, when they are inadequately used there is assocd. **resistance** development. However, indications for treatment initiation are changing continuously and heading towards a conservative approach. In the case of salvage regimens, there are only general guidelines that have not been evaluated in clin. studies. **Resistance** assays have great limitations and their use is very specific. All these factors have made the anti-retroviral therapy a very complicated issue.

IT AIDS (disease)
Anti-AIDS **agents**
(physiopathol. and treatment of acquired immunodeficiency syndrome)

L4 ANSWER 14 OF 20 MEDLINE on STN
AN 2000388374 MEDLINE
DN 20360300 PubMed ID: 10901843
TI [Variability and development of viral populations: assessment and implications].
Variabilite et evolution des populations virales: bilan et implications.
AU Baranowski E; Ruiz-Jarabo C M; Escarmis C; Domingo E
CS Centro de Biologia Molecular Severo Ochoa (CSIC-UAM), Universidad Autonoma de Madrid, Cantoblanco, Espana.. edomingo@cbm.uam.es
SO MEDECINE TROPICALE, (1999) 59 (4 Pt 2) 430-4. Ref: 49
Journal code: 8710146. ISSN: 0025-682X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals; AIDS
EM 200008
ED Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809
AB RNA virus populations consist of complex distributions of closely related but not identical genomes known as viral **quasi-species**. The **quasi-species** concept describes the dynamics of these genomes subjected to a continuous process of variation, competition, and selection. **Quasi-species** dynamics has broad implications not only in the understanding of the molecular mechanisms underlying adaptation of RNA viruses but also in the design of strategies for control and prevention of viral disease. Viral load and genetic heterogeneity have a determinant influence on the adaptation of RNA virus to their environment. Vaccines designed to control diseases caused by highly variable viruses must contain several B and T epitopes to provide an ample and diversified immune response. Similarly, antiviral drugs should be used in combination therapy to minimize selection of **resistant** viruses. The theoretical model of **quasi-species** has opened the way for new antiviral therapies based on augmentation of the mutation rate during replication of viral RNA. Finally the **quasi-species** concept provides the basis for defining the selective factors that could influence the evolution of RNA virus and promote the emergence or reemergence of viral diseases.
AB RNA virus populations consist of complex distributions of closely related but not identical genomes known as viral **quasi-species**

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CT Check Tags: Human; Support, Non-U.S. Gov't
Antibiosis
Antiviral Agents: TU, therapeutic use
English Abstract
Epitopes: IM, immunology
Genome, Viral
Molecular Biology
Mutation: GE, genetics
RNA Virus Infections:. . .

CN 0 (Antiviral **Agents**); 0 (Epitopes); 0 (Viral Vaccines)

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:414400 CAPLUS
DN 129:156495
TI Preclinical characterization of an anti-tat ribozyme for therapeutic application
AU Wang, Li; Witherington, Craig; King, Andrew; Gerlach, Wayne L.; Carr, Andrew; Penny, Ron; Cooper, David; Symonds, Geoff; Sun, Lun-Quan
CS Johnson and Johnson Research Laboratories, Sydney, NSW 2001, Australia
SO Human Gene Therapy (1998), 9(9), 1283-1291
CODEN: HGTHE3; ISSN: 1043-0342
PB Mary Ann Liebert, Inc.
DT Journal
LA English
AB A hammerhead ribozyme retroviral construct, denoted RRz2, targeting the coding region of the human immunodeficiency virus type 1 (HIV-1) tat gene, has shown itself to be effective in a range of test systems. Inhibition of the replication of HIV-1 IIIB and primary drug-**resistant** strains in pooled transduced CEMT4 cells was consistently found to be more than 80% compared with the control-vector transduced cells, whereas a mutant RRz2 gave approx. 45% inhibition. A multiple HIV-1 passage assay showed the absence of emergence of mutations within the specific viral RNA ribozyme target sequences. This lack of generation of ribozyme "escape mutants" occurred despite the almost complete disappearance of a HIV-1 **quasi-species** in the testing virus. When RRz2 was tested in peripheral blood lymphocytes (PBLs) from HIV-1-infected patients, paired anal. showed that cell viability in the ribozyme-transduced HIV-1-infected PBLs was significantly higher than that in the vector-transduced cells. This difference in viability (vector vs. RRz2) was not obsd. in PBLs from non-HIV-1-infected donors. Taken together, these results indicate that the transfer of an anti-HIV-1 ribozyme gene into human T lymphocytes could have major impact on viral replication and T cell viability in the HIV-1-infected individual.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A hammerhead ribozyme retroviral construct, denoted RRz2, targeting the coding region of the human immunodeficiency virus type 1 (HIV-1) tat gene, has shown itself to be effective in a range of test systems. Inhibition of the replication of HIV-1 IIIB and primary drug-**resistant** strains in pooled transduced CEMT4 cells was consistently found to be more than 80% compared with the control-vector transduced cells, whereas a

mutant RRz2 gave approx. 45% inhibition. A multiple HIV-1 passage assay showed the absence of emergence of mutations within the specific viral RNA ribozyme target sequences. This lack of generation of ribozyme "escape mutants" occurred despite the almost complete disappearance of a HIV-1 **quasi-species** in the testing virus. When RRz2 was tested in peripheral blood lymphocytes (PBLs) from HIV-1-infected patients, paired anal. showed that cell viability in the ribozyme-transduced HIV-1-infected PBLs was significantly higher than that in the vector-transduced cells. This difference in viability (vector vs. RRz2) was not obsd. in PBLs from non-HIV-1-infected donors. Taken together, these results indicate that the transfer of an anti-HIV-1 ribozyme gene into human T lymphocytes could have major impact on viral replication and T cell viability in the HIV-1-infected individual.

IT Antiviral **agents**
Gene therapy
Human immunodeficiency virus 1
Retroviral vectors
Retroviridae
(preclin. characterization of anti-tat ribozyme for therapeutic application in HIV-1 infection)

L4 ANSWER 16 OF 20 MEDLINE on STN
AN 2000190254 MEDLINE
DN 20190254 PubMed ID: 10726055
TI Molecular tools for the treatment of hepatitis C.
AU Pawlotsky J M; Gretch D R
CS Department of Bacteriology and Virology, Hopital Henri Mondor, Universite Paris XII, Creteil, France.
SO ANTIVIRAL THERAPY, (1998) 3 (Suppl 3) 45-55. Ref: 77
Journal code: 9815705. ISSN: 1359-6535.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 200004
ED Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000426
AB The treatment of chronic hepatitis C is aimed at eliminating viral replication in order to prevent further evolution towards cirrhosis and hepatocellular carcinoma. Virological parameters include hepatitis C virus (HCV) genotype, qualitative viraemia, quantitative viral load and the characteristics of HCV **quasi-species** heterogeneity. These parameters can be used to predict and monitor the response to therapy, in order to help clinicians to tailor treatment of chronic hepatitis C and to better understand the molecular mechanisms underlying HCV **resistance** to antiviral drugs. Current knowledge on these various issues is reviewed in the present article.
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CT Check Tags: Human
Antiviral Agents: TU, therapeutic use
Biological Markers: AN, analysis
Drug Resistance, Microbial: GE, genetics
Genetic Techniques
Genotype

Hepacivirus: DE, drug effects
Hepacivirus: GE, genetics
*Hepacivirus: IP, isolation & purification
. . .
CN 0 (Antiviral **Agents**); 0 (Biological Markers); 0 (Interferon-alpha); 0 (RNA, Viral)

L4 ANSWER 17 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 1998029634 EMBASE
TI The treatment of chronic viral hepatitis: An update.
AU Sherlock S.
CS S. Sherlock, Department of Surgery, Royal Free Hospital, London NW3 2QG, United Kingdom
SO FORUM - Trends in Experimental and Clinical Medicine, (1997) 7/4 (334-341).
Refs: 51
ISSN: 1121-8142 CODEN: FTCME2
CY Italy
DT Journal; General Review
FS 004 Microbiology
006 Internal Medicine
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB The management of chronic viral hepatitis depends on viral factors and on the status of the host. General host factors include age, duration of infection, the presence of cirrhosis, immunosuppression, concomitant viral infections and alcoholism. Hepatitis B virus integrates with host DNA. Anti-viral therapy is likely to be more successful at the stage of immune clearance where the viral load is low and serum transaminases high. Viral mutations may reduce anti-viral effects. Interferon remains the treatment of choice. Alternative anti-viral drugs such as lamivudine are under trial but viral **resistance** may develop. Immunostimulation by thymosin has not been very successful. Hepatitis C is a variable flavivirus. Anti-viral response is related to genotype. However, viral load is the most important predictor of interferon success. The production of **quasi-species** reduces anti-viral response. Combinations of interferon and ribavirin are giving improved results over interferon alone. Important host factors include the extent of hepatic fibrosis. Immunomodulation is being increasingly investigated. The relationship of hepatitis G virus to chronic hepatitis remains uncertain.
AB . . . reduce anti-viral effects. Interferon remains the treatment of choice. Alternative anti-viral drugs such as lamivudine are under trial but viral **resistance** may develop. Immunostimulation by thymosin has not been very successful. Hepatitis C is a variable flavivirus. Anti-viral response is related to genotype. However, viral load is the most important predictor of interferon success. The production of **quasi-species** reduces anti-viral response. Combinations of interferon and ribavirin are giving improved results over interferon alone. Important host factors include the. . .
CT Medical Descriptors:
*chronic hepatitis: DT, drug therapy
*chronic hepatitis: ET, etiology
***chronic hepatitis: DR, drug resistance**
*virus hepatitis: DT, drug therapy
*virus hepatitis: ET, etiology
***virus hepatitis: DR, drug resistance**
host
age
disease duration
liver cirrhosis: CO, complication
virus infection: CO, complication
immune deficiency

alcoholism
hepatitis b virus
aminotransferase blood level
virus mutation
hepatitis c virus
genotype
virus resistance
liver fibrosis: CO, complication
immunomodulation
hepatitis g virus
human
review
dna: EC, endogenous compound
antivirus agent: CB, drug combination
antivirus agent: DT, drug therapy
aminotransferase: EC, endogenous compound
interferon: CB, drug combination
interferon: DT, drug therapy
lamivudine: DT, drug therapy
thymosin: DT, drug therapy
ribavirin: CB,. . .

L4 ANSWER 18 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 95045961 EMBASE
DN 1995045961
TI [HIV: Recent pathogenic findings: Implications for antiviral therapy]. VIH: IMPLICATIONS DE DONNEES RECENTES DE LA PATHOGENIE POUR LE TRAITEMENT ANTIVIRAL.
AU Perrin L.
CS Laboratoire Central de Virologie, Hopital Cantonal Universitaire,1211 Geneve 14, Switzerland
SO Medecine et Hygiene, (1995) 53/2057 (247-250).
ISSN: 0025-6749 CODEN: MEHGAB
CY Switzerland
DT Journal; (Short Survey)
FS 004 Microbiology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA French
SL English; French
AB The aim of this prospective minireview is to analyse the implications for antiviral therapy of recent pathogenic findings in HIV infection. These include: 1. the detection of viremia, using new assays, at all stages of HIV infection; 2. the identification of lymphoid tissues as the main virus reservoir; 3. the heterogeneity of HIV (**quasi-species**) and its consequence; the rapid emergence of HIV **resistant** strains following antiviral treatment. These elements suggest that, as soon as several antiviral compounds would be available, a new therapeutic strategy should be envisaged including early treatment, polytherapy and monitoring of therapeutic efficacy by quantitative determinations of viremia and detection of mutations associated with drug **resistance** .
AB . . . stages of HIV infection; 2. the identification of lymphoid tissues as the main virus reservoir; 3. the heterogeneity of HIV (**quasi-species**) and its consequence; the rapid emergence of HIV **resistant** strains following antiviral treatment. These elements suggest that, as soon as several antiviral compounds would be available, a new therapeutic. . . early treatment, polytherapy and monitoring of therapeutic efficacy by quantitative determinations of viremia and detection of mutations associated with drug **resistance** .
CT Medical Descriptors:
*human immunodeficiency virus infection: ET, etiology

*human immunodeficiency virus infection: DT, drug therapy
human
human immunodeficiency virus
short survey
viremia
***antivirus agent: DT, drug therapy**
zalcitabine: DT, drug therapy
didanosine: DT, drug therapy
nevirapine: DT, drug therapy
zidovudine: DT, drug therapy

L4 ANSWER 19 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:56933 BIOSIS
DN PREV199698629068
TI **Resistance** to antiretroviral compounds: Implications for the clinical management of HIV infection.
AU Moyle, G. J.
CS Kobler Centre, Chelsea Westminister Hosp., 369 Fulham Road, London SW10 9NH UK
SO Immunology & Infectious Diseases (Oxford), (1995) Vol. 5, No. 3, pp. 170-182.
ISSN: 0959-4957.
DT General Review
LA English
AB Given the high rates of viral replication at all stages of HIV infection and the frequency with which mutations occur during each replication cycle, it is not surprising that a drug-**resistant** virus appears under the selective pressure of antiretroviral therapy. Evidence linking the presence of drug-**resistant quasi-species** to clinical outcome is increasing. Information on patterns of **resistance** and cross-**resistance** to the available antiretroviral **agents** should therefore be considered when deciding how to sequence and/or combine these **agents** to achieve maximal antiviral effects. Analysis of interactions between different mutations, both synergistic and antagonistic, may also be of use when selecting optimum treatment regimens in clinical practice.
TI **Resistance** to antiretroviral compounds: Implications for the clinical management of HIV infection.
AB. . . of HIV infection and the frequency with which mutations occur during each replication cycle, it is not surprising that a drug-**resistant** virus appears under the selective pressure of antiretroviral therapy. Evidence linking the presence of drug-**resistant quasi-species** to clinical outcome is increasing. Information on patterns of **resistance** and cross-**resistance** to the available antiretroviral **agents** should therefore be considered when deciding how to sequence and/or combine these **agents** to achieve maximal antiviral effects. Analysis of interactions between different mutations, both synergistic and antagonistic, may also be of use. . .
IT Miscellaneous Descriptors
ANTAGONISTIC INTERACTION; ANTIRETROVIRAL **AGENTS**; COMBINATION THERAPY; CROSS-**RESISTANCE**; DRUG-DRUG INTERACTION; MUTATION; SYNERGISTIC INTERACTION; VIRAL REPLICATION

L4 ANSWER 20 OF 20 MEDLINE on STN
AN 2001279395 MEDLINE
DN 96700844 PubMed ID: 11362787
TI Antiretroviral drug **resistance**.
AU Japour A J
SO AIDS CLINICAL CARE, (1995 Aug) 7 (8) 63-5, 67.
Journal code: 9000367. ISSN: 1043-1543.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS

EM 199511
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19951107
AB The clinical significance and public health implications for HIV pathogenesis due to **resistance** to antiretroviral **agents** , such as AZT, ddI, ddC, d4T, 3TC, are discussed. Several studies are highlighted, showing that AZT **resistance** is associated with more rapid clinical progression and death. AZT-**resistant** viruses are quite tough, and once established, become the dominant circulating **quasi-species**. Other studies show that the clinical significance of **resistance** to the dideoxynucleosides (ddI, ddC, d4T, and 3TC) remains incompletely understood. The article notes that, despite widespread clinical practice of using combination treatment regimens, no study has proven that combination therapy delays HIV disease progression or death over the long term. Public health considerations include the proven problem of human- to-human transmission of AZT-**resistant** HIV.
TI Antiretroviral drug **resistance**.
AB The clinical significance and public health implications for HIV pathogenesis due to **resistance** to antiretroviral **agents** , such as AZT, ddI, ddC, d4T, 3TC, are discussed. Several studies are highlighted, showing that AZT **resistance** is associated with more rapid clinical progression and death. AZT-**resistant** viruses are quite tough, and once established, become the dominant circulating **quasi-species**. Other studies show that the clinical significance of **resistance** to the dideoxynucleosides (ddI, ddC, d4T, and 3TC) remains incompletely understood. The article notes that, despite widespread clinical practice of. . . disease progression or death over the long term. Public health considerations include the proven problem of human- to-human transmission of AZT-**resistant** HIV.
CT Check Tags: Human
***Antiviral Agents: TU, therapeutic use**
CD4 Lymphocyte Count
Didanosine: TU, therapeutic use
***Drug Resistance, Microbial**
Drug Resistance, Multiple
Drug Therapy, Combination
*HIV Infections: DT, drug therapy
HIV Infections: TM, transmission
*HIV-1: DE, drug effects
HIV-1:. . .
CN 0 (Antiviral **Agents**); 0 (RNA, Viral)

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